Osteoporotic Fractures

iii. Impact Paragraph

The main objective of this thesis was to study the fragility or osteoporotic (OP) fractures, both in the general population and among the patients with rheumatoid arthritis (RA), and in relation to death after fracture and medication use.

Our key messages in **Chapters 5 and 6** are more relevant for the healthcare setting, clinicians and patients with RA, but also possibly for the future therapeutic guidelines. We found that low-dose oral glucocorticoid (GC) therapy was not associated with risk of non-vertebral OP fractures in patients with RA; however, it incurred a 59% increased risk of clinical vertebral fracture. This means an additional two clinical vertebral fractures per 1000 patients with RA in the UK who took low-dose oral GCs in one year. And we know that only one third of vertebral fractures would come into clinical attention, so another four vertebral fractures per 1000 patients with RA in the UK have been caused by low-dose GC therapy in a year and would have been missed in practice. This is an important finding, which warns clinicians that even in RA patients who take low daily GC doses, the risk of vertebral fracture is increased. Furthermore, we found that use of both oral GCs and proton pump inhibitors (PPIs, drugs that reduce stomach acid production) together incurred a 60% higher risk of OP fractures in patients with RA. This means an additional 14 OP fractures per 1000 patients with RA in the UK who took both drugs for one year, compared to non-use of both medications. Thus, more attention should be paid to those RA patients who are prescribed both drugs, with routine fracture risk assessment and proper preventative anti-osteoporotic therapies. This recommendation would be more important for elderly patients, possibly with a more advanced disease, who are at a higher risk of OP fractures due to other risk factors.

The main findings in **Chapters 2 and 4** could be more relevant for policymakers, clinicians and inclusion in therapeutic guidelines. Here, we found a decreasing trend for all four major OP fractures (MOFs) including hip, clinical vertebral, humerus and forearm among women between 1995 and 2010 in Denmark. A slower rate of decrease of hip fracture, steady rate for humerus, and an increasing rate for clinical vertebral fracture was observed among men. Thus, we recommend appropriate screening for OP fractures (by fracture risk assessment and bone mineral density [BMD] measurements if needed), in addition to proper use of anti-osteoporotic treatments not only in postmenopausal women, but also in older men. On the other hand, we showed that there was a clear distinction between long-term and short-term use of oral GCs in risk of hip and clinical

vertebral fracture, in those patients who were taking high daily doses. The threshold of cumulative GC use of 1.0 g prednisolone equivalent dose, as the hallmark of long-term GC therapy, is important for both the prescribing clinician and patients, who due to a chronic inflammatory disease, need long-term GC treatment in moderate to high average daily doses. Therefore, avoiding unnecessary high doses of oral GCs, adequate fracture risk assessment and timely anti-osteoporotic therapy are all recommended in order to avoid the catastrophic consequences of an imminent fracture in such patients.

The findings in **Chapters 3, 6 and 7** would ideally inspire the future research in the respecting field. Based on our findings, oral bisphosphonates (BPs) had apparently no beneficial effect on reducing the number of deaths in patients with a MOF. Oral BPs are highly recommended as first-line treatment in patients with osteoporosis or those who already had an OP fracture, in order to avoid a future fracture. However, our results did not support their hypothetical beneficial effect on hardening of the arteries. Instead, some limitations of the observational studies might explain our findings. Thus, we recommend further studies that could explain the alternative biological mechanisms or some properties of BPs that produce multiple effects, which confer a mortality benefit. Additionally, we did not observe an increasing fracture risk with higher daily doses or longer use of PPIs, which is in contrast to some previous observational studies. To date, few biological mechanisms have been proposed for an effect of PPIs on bone or falling, such as not enough production of stomach acid and calcium malabsorption, or an increased fall risk due to malabsorption of magnesium or vitamin B12, but our results did not support them. This is still an unsolved enigma, and thus an interesting realm for future studies to find a clear and sound mechanism, which can hopefully explain the associations that we and others found in real-world data. Furthermore, we found that biological disease-modifying antirheumatic drugs (bDMARDs) had no independent beneficial effect on reducing the risk of OP fractures in patients with RA. As the only known mechanism of biologic drugs for an effect on bone health is through the inflammatory cycle and considering a "treat-to-target" strategy of RA management in the real-world setting, our results are consenting with the protective effect of bDMARDs on BMD identified by clinical trials. However, more research is recommended to investigate the association between bDMARDs, BMD and OP fracture risk in patients with RA.

Our research projects had also considerable scientific impact. The results of the study in **Chapter 2** were published in one of the top journals in the bone field, i.e., *Osteoporosis International* in 2019. We also presented our findings in poster in the 34th International Conference on Pharmacoepidemiology (ICPE) in August 2018 at Prague, Czech Republic.

We published our results of **Chapter 3** in one of the top journals in the gerontology and geriatrics field, i.e., *Journal of the American Medical Directors Association* in 2020. This project was also orally presented at the Dutch Epidemiological Conference - WEON in July 2019 at Groningen, the Netherlands. The results of the project in **Chapter 4** have been published in *Archives of Osteoporosis* in 2018. The paper from **Chapter 5** has been published in one of the top ranked journals in the field of rheumatology, i.e., *Rheumatology (Oxford)* in 2021. The findings were also orally presented at the American Society for Bone and Mineral Research (ASBMR) 2020 Annual Meeting - virtual edition, oral presentation at the ASBMR Dutch days 2020 - virtual event, and in poster at the ICPE All Access 2020 - virtual event. We published our findings from **Chapter 6** in *Annals of the Rheumatic Diseases* in 2021, which is the rank 1 rheumatology journal in the world. This publication was followed by an especially tailored editorial in the same issue, a couple of correspondences published in the same journal, a lay summary in the British Medical Journal Patient Summaries Blog, and a wide media coverage in medical news services and online bulletins. This project was also presented in poster at the Dutch Epidemiological Conference - WEON in July 2019 in Groningen, the Netherlands, and also in poster at the ASBMR 2020 Annual Meeting - virtual edition. The project in **Chapter 7** has been currently submitted, with a list of target journals in the field of rheumatology, general medicine, and bone. The abstract has been also accepted for plenary poster presentation at the upcoming ASBMR 2021 Annual Meeting.